Cost-effectiveness of cardiac resynchronisation therapy for patients with moderate-to-severe heart failure: a lifetime Markov model.

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Complete List of Authors:	Neyt, Mattias; Belgian Health Care Knowledge Centre (KCE) Stroobandt, Serge; Belgian Health Care Knowledge Centre (KCE) Obyn, Caroline; Belgian Health Care Knowledge Centre (KCE) Camberlin, Cécile; Belgian Health Care Knowledge Centre (KCE) Devriese, Stephan; Belgian Health Care Knowledge Centre (KCE) De Laet, Chris; Belgian Health Care Knowledge Centre (KCE) Van Brabandt, Hans; Belgian Health Care Knowledge Centre (KCE)
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Cost-effectiveness of cardiac resynchronisation therapy for patients with moderate-to-severe heart failure.

Mattias Neyt, Serge Stroobandt, Caroline Obyn,

Cécile Camberlin, Stephan Devriese,

Chris De Laet, Hans Van Brabandt

Belgian Health Care Knowledge Centre (KCE), Brussels, Belgium

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Corresponding author

Mattias Neyt, PhD,

Belgian Health Care Knowledge Centre (KCE),

Kruidtuinlaan, 55

1000 Brussels

mattias.neyt@kce.fgov.be

Tel: +32(0)2/287.33.39

Fax: +32(0)2/287.33.85

ABSTRACT

Objective: To assess the cost-effectiveness of cardiac resynchronisation therapy (CRT) both with CRT-P (biventricular pacemaker only) and CRT-D (biventricular pacemaker with defibrillator) in patients with New York Heart Association (NYHA) functional class III/IV from a Belgian health care payer perspective.

Methods: A lifetime Markov model was designed to calculate the cost-utility of both interventions. In the reference case, the treatment effect is based on the COMPANION trial. Costs are based on real-world data. Pharmacoeconomic guidelines were applied, including probabilistic modelling and sensitivity analyses.

Results: Compared with optimal medical treatment, on average 1.31 quality-adjusted life-years (QALY) are gained with CRT-P at an additional cost of €14,700, resulting in an incremental cost-effectiveness ratio (ICER) of about €11,200/QALY. As compared to CRT-P, CRT-D treatment adds on average an additional 0.55 QALYs at an extra cost of €30,900 resulting in an ICER of €57,000/QALY. This result was very sensitive to the incremental clinical benefit of the defibrillator function on top of CRT.

Conclusions: Based on efficiency arguments, CRT-P can be recommended for NYHA class III and IV patients if there is a willingness to pay more than €11,000/QALY. Even though CRT-D may offer a survival benefit over CRT-P, the incremental clinical benefit appears to be too marginal to warrant a three times higher device price for CRT-D. Further clinical research should focus on the added value of CRT-D over CRT-P.

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome that can result from any cardiac disorder that impairs the ability of the heart to function as a pump. Patients that are clinically stable but suffer from a severely reduced contractile function (Left Ventricular Ejection Fraction; LVEF≤35%) remain at high risk of sudden cardiac death (SCD).[1] Approximately 50% of deaths in patients with HF are due to a sudden cardiac arrest.[2] Therefore, HF patients are potential candidates for treatment with an implantable cardioverter defibrillator (ICD). Selected patients with end-stage HF, who remain symptomatic despite optimal pharmacologic treatment (OPT), could also be considered for cardiac resynchronisation therapy (CRT),[3] its cost-effectiveness constituting the topic of this study.

CRT can be offered by two types of devices: biventricular pacemakers, also called CRT-P devices, and biventricular defibrillators, also known as CRT-D devices. CRT aims to improve the heart's contractile function by electrically stimulating the cardiac chambers, thus synchronising their contraction. A CRT-D device offers the additional ability to stop life-threatening ventricular arrhythmias preventing SCD.

The Belgian Health Care Knowledge Centre (KCE), an independent semi-governmental institution, conducted a health technology assessment (HTA) about the clinical effectiveness and cost-effectiveness of CRT for HF patients.

METHODS

A Markov simulation model was developed in order to evaluate the cost-effectiveness of CRT-P and CRT-D therapy. Both cost-effectiveness, expressing results in additional expenses for a life-year gained (LYG), and cost-utility analyses using quality-adjusted life-years (QALY) gained, were performed.

The analysis includes direct health care costs from the perspective of the health care payer. In Belgium this constitutes payments from the government's health care budget as well as patients' co-payments. Dealing with a chronic disease, a lifetime horizon was also applied. Future costs and benefits were discounted at a rate of 3% and 1.5%, respectively, according to national pharmacoeconomic guidelines.[4] In scenario analyses, these rates were subsequently changed.

To capture parameter uncertainty, input variables are modelled as probabilistic values. The choice of distribution depends on the characteristics of the input variables.[5] Due to the central limit theorem, parameters can be sampled from a normal distribution with the appropriate confidence interval around the mean. The beta distributions are used for parameters constrained to the interval 0-1 (such as QoL values). Gamma distributions are used for skewed variables. 1000 Latin hypercube simulations were generated in MicroSoft Excel using the @Risk (Palisade Corporation) add-in program.

The interventions of interest, CRT-P and CRT-D, are always provided on top of optimal pharmacologic treatment (OPT). Hence, OPT is the initial comparator for both CRT-P and CRT-D to determine their position on the cost-effectiveness plane (which presents the difference in effects on the x-axis and differences in costs on the y-axis). The incremental cost-effectiveness ratios (ICERs), comparing incremental costs with incremental effects, were calculated on the efficiency frontier. According to health economic theory,[5] ICERs should be calculated on this frontier comparing an intervention with the previous most cost-effective intervention. To be able to interpret results cost-effectiveness acceptability curves are presented, expressing the probability that an intervention is considered cost-effective (y-axis) depending on the willingness to pay (WTP) for an additional QALY (x-axis).

Model

The model simulates a hypothetical cohort of 1,000 CRT-eligible patients. The type of participants considered were patients with moderate-to-severe heart failure (NYHA class III-IV) with low ejection fraction (≤35%) and delayed intraventricular conduction evidenced by a wide QRS complex. In the base case scenario, the patient population is 67 years old and 67.4% of them is male, corresponding to the patients that were enrolled in the COMPANION trial.[6] Baseline employment rates can safely assumed to be low in this population and therefore indirect productivity costs were ignored.

In the literature review on effectiveness of CRT,[7] all-cause mortality and hospitalisation due to heart failure were considered as primary endpoints. This is reflected in the Markov model with monthly cycles (Figure 1). Patients receiving a CRT-P/D are subject to a procedure-related mortality risk. Furthermore, every month, patients are at risk of all-cause death. Survivors will receive OPT for that month, are at risk of hospitalisation due to heart failure and may receive an upgrade (either from OPT to ICD or from CRT-P to CRT-D).

Insert Figure 1 around here

Mortality

Randomised trials have shown that both CRT-P and CRT-D, in addition to OPT prolong life in subsets of patients with NYHA class III/IV heart failure.[6, 8] The results of the COMPANION trial[6] were used to model the treatment effect. This happens to be the only trial that compared CRT-P+OPT as well as CRT-D+OPT versus OPT, allowing an indirect comparison to be made between CRT-P and CRT-D. Based on this trial, the monthly probability of death was 0.017 for

the OPT group.[9] Applying the reduced mortality risk of 24% (p=0.059) and 36% (p=0.003) for CRT-P and CRT-D resulted in a monthly probability of 0.013 and 0.011, respectively. A normal distribution was used to account for the uncertainty around these numbers.

In the COMPANION trial, the median follow-up time was 14.8 months, 16.5 months, and 16.0 months, for the OPT, CRT-P and CRT-D group, respectively.[6] In our model, extrapolation starts after month 16 for the three intervention groups. The monthly probability of death was made time-dependent by adding the absolute monthly increase in mortality of the normal age- and gender-adjusted Belgian population.

In a systematic review of clinical trials on CRT,[10] 21 peri-operative deaths were counted among 2757 patients (Table 1). This procedure-related mortality risk of both CRT-P and CRT-D implantations is accounted for by applying a beta-distribution. However, in order to avoid double counting, monthly mortality rates during the first year were slightly adjusted downwards, keeping the original trial-based one-year mortality at the same level.

Table 1: Input variables for the Markov model

	Mean	Range (95%CI)*		Distribution	Source
		2.5%	97.5%		
Characteristics of the population					
Start age of the cohort	67 years	/	/	/	COMPANION trial[6]
Proportion male	67%	/	/	/	
Mortality (monthly)					
OPT	0.017	/	/	/	Feldman et al., 2005[9]
CRT-P	0.01292	0.00868	0.01716	Normal	Feldman et al.,
CRT-D	0.01088	0.00801	0.01375	Normal	2005[9]; COMPANION

					trial[6] and own calculations.
Procedure related mortality					
		alpha	beta		
Perioperative deaths	0.76%	21	2736	Beta	Fox et al., 2007[10]
Hospitalizations (Monthly probability of hospital admission)					
OPT	0.117	/	/	/	Feldman et al., 2005[9]
CRT-P	0.098	0.0707	0.1253	Normal	Feldman et al., 2005[9] and own calculations
CRT-D	0.097	0.0704	0.1236	Normal	
Length of stay					
Primo implantation	7.34	6.2	8.48	Normal	Belgian database
Replacement	4.47	3.53	5.41	Normal	
Utility weights					
OPT	0.68	0.63	0.73	Beta	Cleland et al., 2005[8]; Calvert et al., 2005[11]; Feldman et al., 2005[9] and own assumptions.
CRT-P	0.78	0.73	0.83	Beta	
CRT-D	0.78	0.73	0.83	Beta	
Hospitalization primo implantation or replacement	0.46	0.41	0.51	Beta	
Costs					
Primo implantation					
CRT-P	9,398 €	8,859 €	9,936 €	Normal	Belgian database, reimbursement tariffs and own adaptions.
CRT-D	23,380 €	22,842 €	23,919 €	Normal	
ICD	27,261 €	26,867 €	27,658 €	Gamma	KCE report ICDs[12]
Replacement					
CRT-P	9,061 €	8,267 €	9,856 €	Normal	Belgian database,

CRT-D	21,905 €	21,111 €	22,700 €	Normal	reimbursement tariffs and own adaptions.
Hospitalization	5,777 €	1,129 €	17,807 €	Gamma	Technical cel (APR-DRG 194 "heart failure")
Follow-up medication (monthly cost)	30.88 €	29.85 €	31.82 €	Beta for volumes	Belgian database (volumes) and BCFI (prices)
Follow-up visits (average monthly cost)	OPT	CRT-P	CRT-D		
GP, cardiologist (ECG, echo, integrity check)	52.98 €	71.87 €	90.77 €	Beta for volumes	Expert opinion
Cross-over/upgrade					
OPT - ICD	0.0015	-50%	+50%	Uniform	Bond et al., 2009[13]
CRT-P - CRT-D	0.0005	-50%	+50%	Uniform	

*: 95%CI, unless otherwise mentioned

APR-DRG: All Patient Refined Diagnosis Related Groups; BCFI: Belgian Centre for Pharmacotherapeutic Information; CRT-P/D: cardiac resynchronisation therapy (CRT) both with pacemaker (CRT-P) and additionally including a defibrillator (CRT-D); ECG: electrocardiogram; GP: general practitioner; ICD: implantable cardioverter defibrillator; OPT: optimal pharmacologic treatment.

Hospitalisations

Hospitalisation rates are based on the COMPANION trial as reported by Feldman et al.[9] The monthly probability of hospital admission was estimated to be 0.117 for the OPT group, 0.098 (p=0.172) for CRT-P and 0.097 (p=0.141) for the CRT-D group (Table 1). The uncertainty around these numbers is accounted for with a normal distribution. In our reference case, the

hospitalisation rates were assumed to be constant over the full time horizon. This was subsequently altered during a scenario analysis.

Costs

An average cost of €23,380 (95%CI of the mean 22,842 - 23,919) for a primo CRT-D implantation was obtained from the actual hospital billing data of 342 Belgian CRT-D primo implantations that occurred during the period 2008 until mid 2009. This cost is modelled with a normal distribution (Table 1). The implantation cost of a primo CRT-P was inferred by subtracting the cost difference from the CRT-D implantation cost. Based on the reimbursement tariffs, the price for CRT-P and CRT-D, including leads, is €7,187 and €21,170, respectively.[7] As such, the average cost for CRT-P implantation was €9,398 (95%CI of the mean €8,859 - 9,936).

A similar approach was used for the cost of a device replacement. Based on Belgian data (n = 121), the CRT-D replacement cost was €21,905 (95%CI of the mean €21,111 - €22,700). With a price difference between the CRT-P and CRT-D device of €12,844, this amounts to €9,061 (95%CI of the mean €8,267 - €9,856) for CRT-P. Service life was equalled to the average of expert opinion-based service lives encountered in other studies,[9, 10] i.e. 75 months for CRT-P and 60 months for CRT-D. This assumption was altered in various scenario analyses.

Data from the Belgian Technical Cell (www.tct.fgov.be) served as the source for obtaining hospitalisation costs. The cost for “APR-DRG 194 Heart Failure” was on average €5,529 (90%CI 1,233 - 14,132) per hospitalisation based on data from more than 19,000 hospitalisation episodes in the year 2007. This cost was included as a gamma distribution and adjusted to 2008 values (Consumer Price Index of 104.5% or on average €5,777) (Table 1).

Prescription medication use was taken from the available data on the Belgian CRT population, right before implantation.[7] The amount and type of drugs are assumed to remain the same

after implantation on a per patient base. Prescription medication costs are based on the cheapest formulation as indicated by the Belgian Centre for Pharmacotherapeutic Information, www.bcfi.be (accessed November 2010). The percentage of users is included as a beta distribution with parameters reflecting the values of the Belgian CRT sample. The average monthly medication cost is €30.88 per patient (95%CI 29.85 - 31.82) (Table 1). Details are presented as data supplement.

Based on expert opinion, we assumed patients consulted their cardiologist four times a year at €34.02 per consultation, and received GP visits at €19.37 per visit for the remaining eight months of the year. This was modelled applying a beta distribution with the minimum and maximum ±50% above/under the average. For every consultation an ECG (€16.94) and echocardiographic examination (€69.24) were billed as well. A CRT integrity check was also counted at €56.68 for CRT-P and €113.36 for CRT-D systems. As such, the monthly visit costs for OPT, CRT-P and CRT-D are respectively €52.98, €71.87 and €90.77 (Table 1).

Finally, the model also included a possibility for cross-over or upgrade. Patients in the OPT group could receive an ICD, whereas patients in the CRT-P group could be upgraded to CRT-D. Medical therapy and CRT recipients received an ICD in the model of Bond et al.[13]/Fox et al.[10] as soon as they survived a serious arrhythmic event. Based on their model, we included upgrade probabilities of 0.0015 and 0.0005 per month for the OPT and CRT-P group, respectively (Table 1). These probabilities were multiplied with a uniform distribution (0.5-1.5) to reflect the large uncertainty around these numbers. The cost of an ICD implantation was based on another Belgian ICD study and amounts to €27,261 (95%CI 26,867 - 27,658)[12]. We preferred not to index this cost since the reimbursement price for the device has decreased since then. For an upgrade from CRT-P to CRT-D, the cost of a CRT-D replacement was taken into account. Cross-over- or upgrade-related procedural deaths were not explicitly accounted for since we assumed these to be reflected in the initial intention-to-treat mortality rates.

Utilities

Utility values are based on the studies of Cleland et al.,[8] Calvert et al.[11] and Feldman et al.[9] The baseline out-of-hospital utility was set to 0.68 (Table 1).[9] 2) The utility improvement in the CRT-P/D groups was estimated to amount to 0.1,[8, 9, 11] resulting in a utility weight of 0.78. An average utility weight of 0.46 was incorporated during the hospital stay of the initial and replacement implantations, which averaged respectively 7.34 days and 4.47 days in the Belgian CRT sample (Table 1). Details of the studies that support these utility values are briefly outlined in the data supplement on utilities.

Sensitivity and scenario analyses

Results of the probabilistic model are presented on the cost-effectiveness plane and as cost-effectiveness acceptability curves. Several scenario analyses are performed for mortality rates, hospitalizations, discount rates, and device service life.

RESULTS

According to the model, the undiscounted life expectancy is 4.6 years for the OPT group. CRT-P increases life expectancy with 1.31 years (95%CI -0.04 – 3.21). CRT-D adds another 0.8 years (95%CI -1.40 – 2.95) on top of CRT-P. If quality of life changes are taken into account, this becomes 1.47 QALYs (95%CI 0.39 – 3.00) and 0.63 QALYs (95%CI -1.18 – 2.38), respectively. This results in a discounted incremental effect adjusted for quality of life of 1.31 QALYs (95%CI 0.36 – 2.64) and 0.55 QALYs (95%CI -1.02 – 2.07), respectively.

The average incremental cost is less than €15,000 for CRT-P versus OPT. In combination with the discounted gain in life expectancy, this results in an average ICER of about €12,800/LYG. If QoL-adjustments are taken into account, this becomes €11,200/QALY gained. The ICER of CRT-D versus OPT is higher than that of CRT-P versus OPT, thus calculating the ICER on the

efficiency frontier, CRT-P becomes its economic justified comparator. The total incremental cost of CRT-D versus CRT-P is on average more than €30,000. The ICER becomes on average €44,100/LYG or €56,600/QALY gained. More details and confidence intervals are available in the data supplements.

Figure 2 shows the cost-effectiveness plane; on top both CRT-P and CRT-D versus OPT (incremental effects expressed as QALYs gained), while at the bottom CRT-P becomes the comparator for CRT-D. The scatter plot clearly shows the impact of considering CRT-P as the comparator for CRT-D.

Insert Figure 2 around here

For each of the 1000 simulations, ICERs are calculated, allowing to express results as the probability that the three alternatives are considered cost-effective depending on the WTP for a QALY. Figure 3 shows these cost-effectiveness acceptability (CEA)-curves. OPT is the preferred option if the WTP for a QALY gained is less than €11,000. Above this threshold, CRT-P is most probably the best alternative with a probability of about 90% at a threshold of about €21,000 per QALY gained. If this willingness is more than €30,000, the probability that OPT is chosen is almost nil. This WTP has to increase to more than €56,000 per QALY gained for CRT-D to have a probability of more than 50% for being considered a cost effective alternative. The fact that there is still a probability that CRT-P is cost effective at this high WTP threshold illustrates the uncertainty around the incremental benefit of CRT-D versus CRT-P.

Insert Figure 3 around here

Scenario analyses on mortality, hospitalisation and discount rates revealed that the results for CRT-P versus OPT can be considered robust. The difference in cost-effectiveness between CRT-P and CRT-D is mainly determined by the threefold higher device price for a CRT-D versus CRT-P. Furthermore, at current price differences between CRT-P and CRT-D, small incremental benefits of CRT-D versus CRT-P result in relatively unfavourable cost-effectiveness ratios for CRT-D. For the results of these scenario analyses, we refer to the data supplements and the full HTA report.[7]

DISCUSSION

In previously published health economic evaluations of CRT, ICERs vary considerably, both for CRT-P (from €3,600[14] to $108,000[15] per QALY gained) and for CRT-D (from £40,160[13] to $172,308[9] per QALY gained). Since costs and resource use may widely vary across countries and because of methodological considerations, results might not be applicable to Belgian practice, and thus it was decided to perform a health economic evaluation of CRT from a Belgian health care payer perspective.

Compared with OPT, on average 1.31 QALYs are gained with CRT-P at an additional cost of €14,700, resulting in an ICER of about €11,200/QALY. Compared to CRT-P, CRT-D provides on average 0.55 QALYs at an extra cost of €30,900 or an average ICER of €57,000/QALY. Reimbursing CRT-P can thus be considered as efficient use of limited sources if the WTP is higher than €11.000 for a QALY gained. Current evidence is insufficient to show the superiority of CRT-D over CRT-P. With a threefold higher device cost, CRT-D's cost-effectiveness is questionable.

All economic evaluations, including our own model, are subject to a number of common limitations. Firstly, there is the short-term follow-up of the trials necessitating extrapolation assumptions. Secondly, the economic evaluations are limited by the external validity of the trial results. The technical skills of providers, patient selection and differences in the optimal treatment regimen may vary in real world practice and affect the clinical effectiveness of the therapy.

Furthermore, economic evaluations are limited by the way QoL was included. Generic utility instruments to measure QoL are not systematically used in trials. Several studies measure utility values by NYHA class rather than for the different treatment groups. The validity of this approach depends on a double link. Firstly, the link between the treatment and the outcome (in terms of NYHA class, which is a subjective measure for functional disability). Secondly, the link between NYHA class and QoL. Such indirect determination bears an increased risk of inaccuracy. It would be useful to include more systematically a generic utility instrument to measure QoL in trials. Calvert et al.[11] showed that the EQ-5D appears to be an acceptable valid measure for use in patients with HF. Nevertheless, a minority of studies include such an instrument in addition to disease-specific instruments in their research protocol.

In our assessment of the cost-utility of CRT we found that, compared to OPT, CRT-P has a better cost-effectiveness ratio than CRT-D. Therefore, the relevant comparator for assessing the cost-effectiveness of CRT-D, which is marginally and non-significantly more efficacious regarding mortality than CRT-P, is therefore CRT-P. A direct comparison of the performance of CRT-P vs. CRT-D has not yet been performed. A Bayesian network meta-analysis of randomised controlled trials indicated that evidence is insufficient to show the superiority of CRT-D over CRT-P in these patients.[16] The added value of CRT-D versus CRT-P in patients with moderate to severe HF is unknown and may be an interesting topic for further research, especially because of the threefold higher price for a CRT-D device versus CRT-P.

CONTRIBUTOR STATEMENT

MN carried out the economic analysis and drafted the paper. SS and CO performed an economic literature review to collect relevant data. SD prepared the demand for the Belgian commission for the protection of personal data. CC and SD analysed the Belgian data. CD and HV provided medical advice and performed a medical literature review in search for relevant data. MN, SS, CD and HV participated in revising the draft paper. MN is guarantor for the paper.

COMPETING INTERESTS

The authors have no conflicts of interest relevant to the content of this study.

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IMAGES

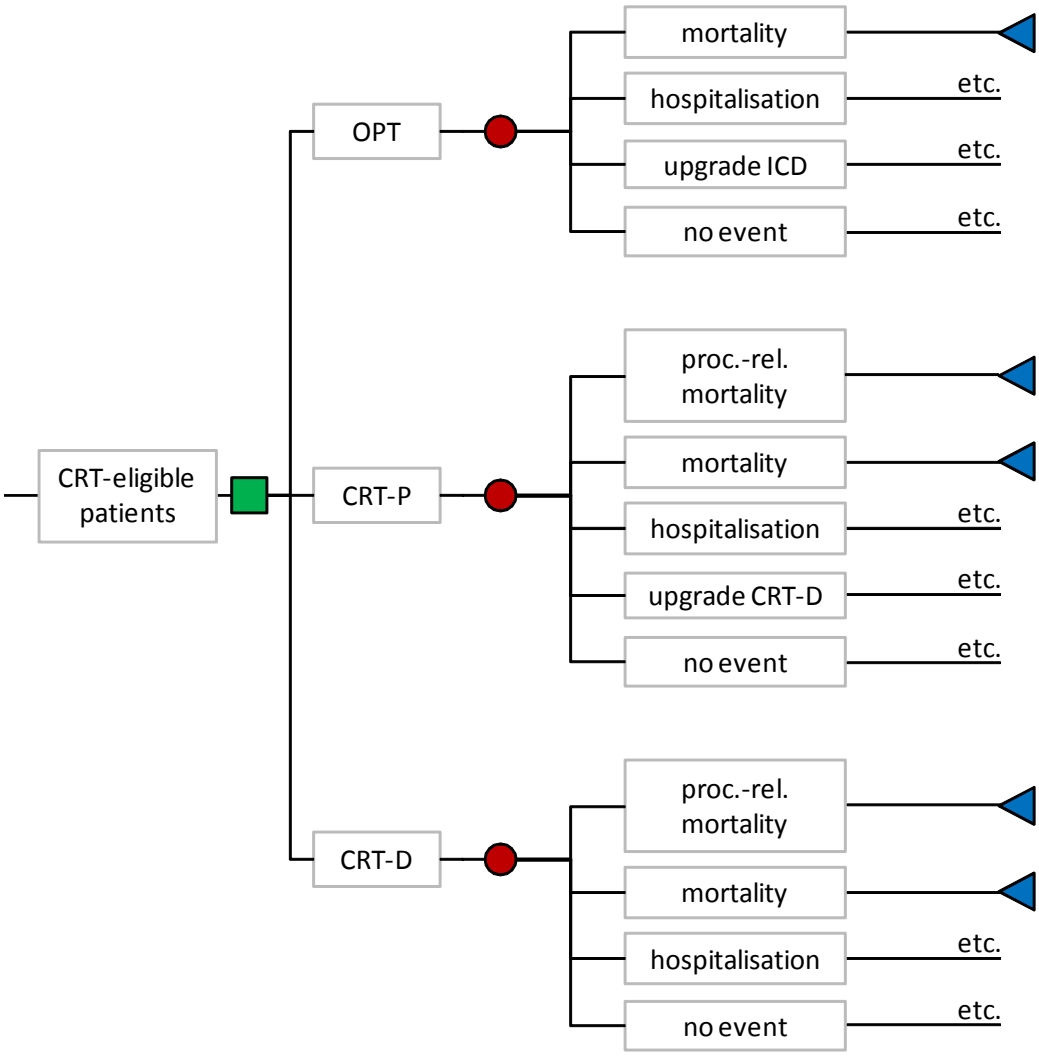
Uploaded as separate files:

Figure 1: CRT-P/D decision model

Figure 2: Cost-effectiveness planes CRT-P/D versus OPT (top) and CRT-D versus CRT-P (bottom)

Figure 3: Cost-effectiveness acceptability curves for the three alternative treatment options (OPT, CRT-P and CRT-D)

Figure 1: CRT-P/D decision model



CRT-P/D: cardiac resynchronization therapy (CRT) both with pacemaker (CRT-P) and additionally including a defibrillator (CRT-D); ICD: implantable cardioverter defibrillator; OPT: optimal medical treatment; proc.-rel. mortality: procedure-related mortality.

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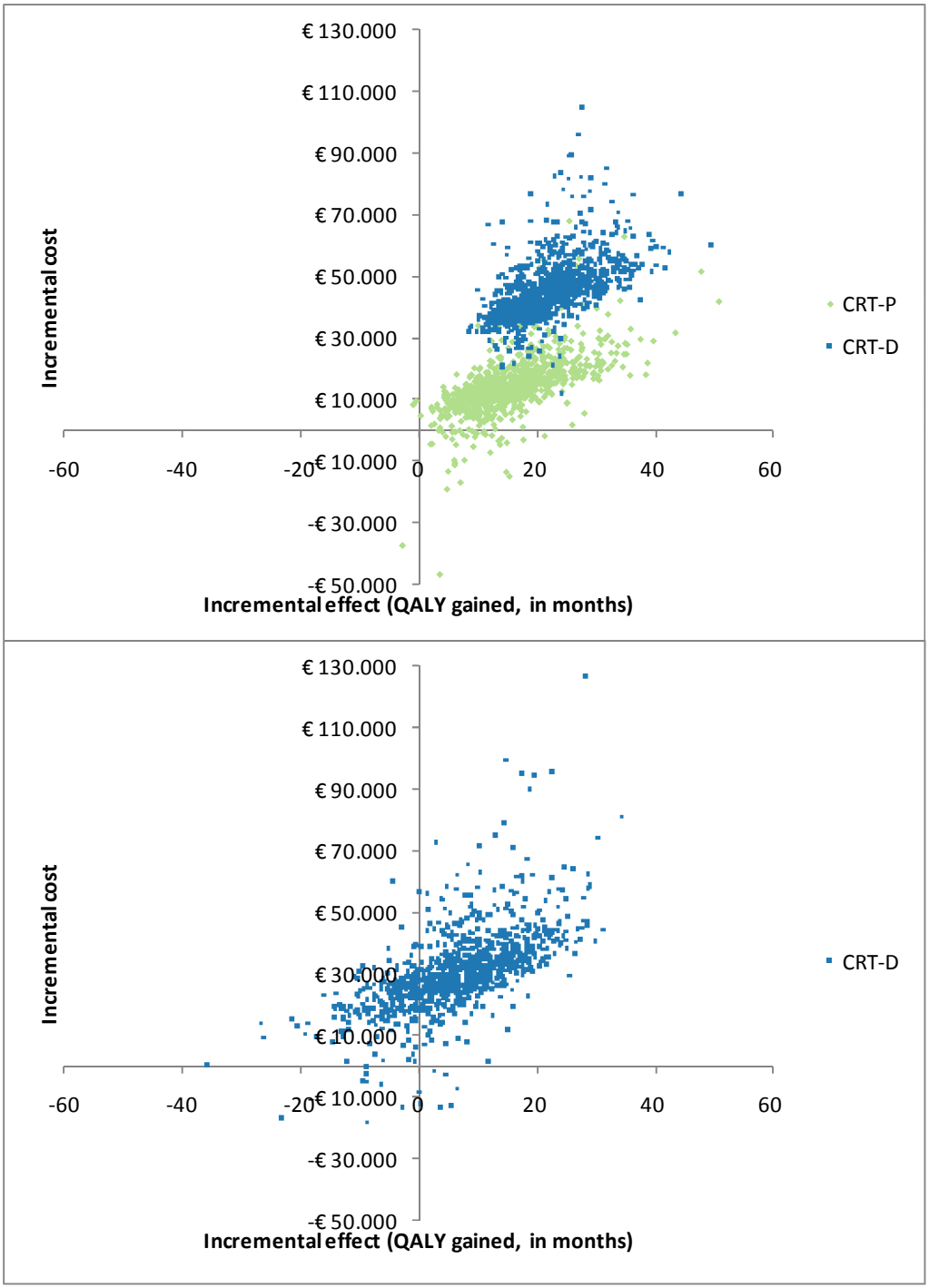
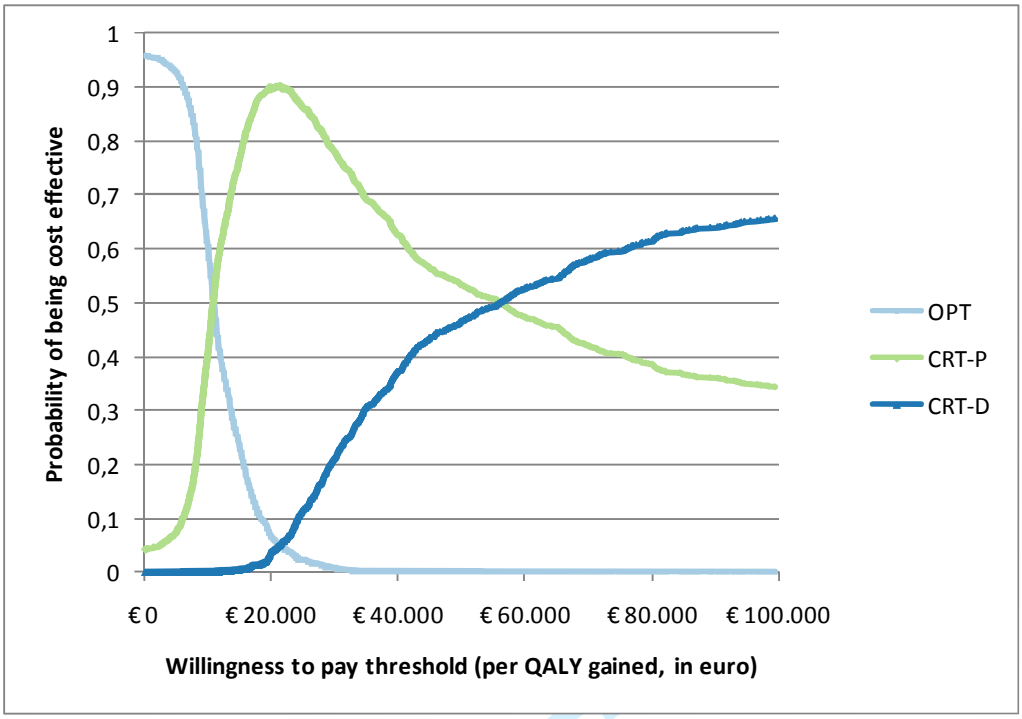


Figure 3: Cost-effectiveness acceptability curves for the three alternative treatment options (OPT, CRT-P and CRT-D)



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Complete List of Authors:	Neyt, Mattias; Belgian Health Care Knowledge Centre (KCE) Stroobandt, Serge; Belgian Health Care Knowledge Centre (KCE) Obyn, Caroline; Belgian Health Care Knowledge Centre (KCE) Camberlin, Cécile; Belgian Health Care Knowledge Centre (KCE) Devriese, Stephan; Belgian Health Care Knowledge Centre (KCE) De Laet, Chris; Belgian Health Care Knowledge Centre (KCE) Van Brabandt, Hans; Belgian Health Care Knowledge Centre (KCE)
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Cost-effectiveness of cardiac resynchronisation therapy for patients with moderate-to-severe heart failure: a lifetime Markov model.

Mattias Neyt, Serge Stroobandt, Caroline Obyn,

Cécile Camberlin, Stephan Devriese,

Chris De Laet, Hans Van Brabandt

Belgian Health Care Knowledge Centre (KCE), Brussels, Belgium

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Corresponding author

Mattias Neyt, PhD,

Belgian Health Care Knowledge Centre (KCE),

Kruidtuinlaan, 55

1000 Brussels

mattias.neyt@kce.fgov.be

Tel: +32(0)2/287.33.39

Fax: +32(0)2/287.33.85

ABSTRACT

Objective: To assess the cost-effectiveness of cardiac resynchronisation therapy (CRT) both with CRT-P (biventricular pacemaker only) and CRT-D (biventricular pacemaker with defibrillator) in patients with New York Heart Association (NYHA) functional class III/IV from a Belgian health care payer perspective.

Methods: A lifetime Markov model was designed to calculate the cost-utility of both interventions. In the reference case, the treatment effect was based on the COMPANION trial. Costs were based on real-world data. Pharmacoeconomic guidelines were applied, including probabilistic modelling and sensitivity analyses.

Results: Compared with optimal medical treatment, on average 1.31 quality-adjusted life-years (QALY) are gained with CRT-P at an additional cost of €14,700, resulting in an incremental cost-effectiveness ratio (ICER) of about €11,200/QALY. As compared to CRT-P, CRT-D treatment adds on average an additional 0.55 QALYs at an extra cost of €30,900 resulting in an ICER of €57,000/QALY. This result was very sensitive to the incremental clinical benefit of the defibrillator function on top of CRT.

Conclusions: Based on efficiency arguments, CRT-P can be recommended for NYHA class III and IV patients if there is a willingness to pay more than €11,000/QALY. Even though CRT-D may offer a survival benefit over CRT-P, the incremental clinical benefit appears to be too marginal to warrant a three times higher device price for CRT-D. Further clinical research should focus on the added value of CRT-D over CRT-P.

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome that can result from any cardiac disorder that impairs the ability of the heart to function as a pump. Patients that are clinically stable but suffer from a severely reduced contractile function (Left Ventricular Ejection Fraction; LVEF≤35%) remain at high risk of sudden cardiac death (SCD).[1] Approximately 50% of deaths in patients with HF are due to a sudden cardiac arrest.[2] Therefore, HF patients are potential candidates for treatment with an implantable cardioverter defibrillator (ICD). Selected patients with end-stage HF, who remain symptomatic despite optimal pharmacologic treatment (OPT), could also be considered for cardiac resynchronisation therapy (CRT).[3] The scope of this manuscript is to calculate CRT's cost-effectiveness in order to provide reimbursement advice to the Belgian competent authorities.

CRT can be offered by two types of devices: biventricular pacemakers, also called CRT-P devices, and biventricular defibrillators, also known as CRT-D devices. CRT aims to improve the heart's contractile function by electrically stimulating the cardiac chambers, thus synchronising their contraction. A CRT-D device offers the additional ability to stop life-threatening ventricular arrhythmias preventing SCD.

The Belgian Health Care Knowledge Centre (KCE), an independent semi-governmental institution, conducted a health technology assessment (HTA) about the clinical effectiveness and cost-effectiveness of CRT for HF patients.

METHODS

A Markov simulation model was developed in order to evaluate the cost-effectiveness of CRT-P and CRT-D therapy. Both cost-effectiveness, expressing results in additional expenses for a life-

year gained (LYG), and cost-utility analyses using quality-adjusted life-years (QALY) gained, were performed.

The analysis included direct health care costs from the perspective of the health care payer. In Belgium this constitutes payments from the government's health care budget as well as patients' co-payments. Dealing with a chronic disease, a lifetime horizon was also applied. Future costs and benefits were discounted at a rate of 3% and 1.5%, respectively, according to national pharmacoeconomic guidelines.[4] In scenario analyses, these rates were subsequently changed.

To capture parameter uncertainty, input variables were modelled as probabilistic values. The choice of distribution depends on the characteristics of the input variables.[5] Due to the central limit theorem, parameters can be sampled from a normal distribution with the appropriate confidence interval around the mean. The beta distributions are used for parameters constrained to the interval 0-1 (such as QoL values). Gamma distributions are used for skewed variables. 1000 Latin hypercube simulations were generated in MicroSoft Excel using the @Risk (Palisade Corporation) add-in program.

The interventions of interest, CRT-P and CRT-D, are always provided on top of optimal pharmacologic treatment (OPT). Hence, OPT is the initial comparator for both CRT-P and CRT-D to determine their position on the cost-effectiveness plane (which presents the difference in effects on the x-axis and differences in costs on the y-axis). The incremental cost-effectiveness ratios (ICERs), comparing incremental costs with incremental effects, were calculated on the efficiency frontier. According to health economic theory,[5] ICERs should be calculated on this frontier comparing an intervention with the previous most cost-effective intervention. To be able to interpret results cost-effectiveness acceptability curves are presented, expressing the

probability that an intervention is considered cost-effective (y-axis) depending on the willingness to pay (WTP) for an additional QALY (x-axis).

Model

The model simulated a hypothetical cohort of 1,000 CRT-eligible patients. The type of participants considered were patients with moderate-to-severe heart failure (NYHA class III-IV) with low ejection fraction (≤35%) and delayed intraventricular conduction evidenced by a wide QRS complex. In the base case scenario, the patient population was 67 years old and 67.4% of them was male, corresponding to the patients that were enrolled in the COMPANION trial.[6] Baseline employment rates can safely assumed to be low in this population and therefore indirect productivity costs were ignored.

In the literature review on effectiveness of CRT,[7] all-cause mortality and hospitalisation due to heart failure were considered as primary endpoints. This was reflected in the Markov model with monthly cycles (Figure 1). Patients receiving a CRT-P/D were subject to a procedure-related mortality risk. Furthermore, every month, patients were at risk of all-cause death. Survivors received OPT for that month, were at risk of hospitalisation due to heart failure and could receive an upgrade (either from OPT to ICD or from CRT-P to CRT-D).

Insert Figure 1 around here

Mortality

Randomised trials have shown that both CRT-P and CRT-D, in addition to OPT prolong life in subsets of patients with NYHA class III/IV heart failure.[6, 8] The results of the COMPANION trial[6] were used to model the treatment effect. This was the only trial that compared CRT-

P+OPT as well as CRT-D+OPT versus OPT, allowing an indirect comparison to be made between CRT-P and CRT-D. Based on this trial, the monthly probability of death was 0.017 for the OPT group.[9] Applying the reduced mortality risk of 24% (p=0.059) and 36% (p=0.003) for CRT-P and CRT-D resulted in a monthly probability of 0.013 and 0.011, respectively. A normal distribution was used to account for the uncertainty around these numbers.

In the COMPANION trial, the median follow-up time was 14.8 months, 16.5 months, and 16.0 months, for the OPT, CRT-P and CRT-D group, respectively.[6] In our model, extrapolation started after month 16 for the three intervention groups. The monthly probability of death was made time-dependent by adding the absolute monthly increase in mortality of the normal age- and gender-adjusted Belgian population.

In a systematic review of clinical trials on CRT,[10] 21 peri-operative deaths were counted among 2757 patients (Table 1). This procedure-related mortality risk of both CRT-P and CRT-D implantations was accounted for by applying a beta-distribution. However, in order to avoid double counting, monthly mortality rates during the first year were slightly adjusted downwards, keeping the original trial-based one-year mortality at the same level.

Table 1: Input variables for the Markov model

	Mean	Range (95%CI)*		Distribution	Source
		2.5%	97.5%		
Characteristics of the population					
Start age of the cohort	67 years	/	/	/	COMPANION trial[6]
Proportion male	67%	/	/	/	
Mortality (monthly)					
OPT	0.017	/	/	/	Feldman et al., 2005[9]

CRT-P	0.01292	0.00868	0.01716	Normal	Feldman et al., 2005[9]; COMPANION trial[6] and own calculations.
CRT-D	0.01088	0.00801	0.01375	Normal	
Procedure related mortality					
		alpha	beta		
Perioperative deaths	0.76%	21	2736	Beta	Fox et al., 2007[10]
Hospitalizations (Monthly probability of hospital admission)					
OPT	0.117	/	/	/	Feldman et al., 2005[9]
CRT-P	0.098	0.0707	0.1253	Normal	Feldman et al., 2005[9] and own calculations
CRT-D	0.097	0.0704	0.1236	Normal	
Length of stay					
Primo implantation	7.34	6.2	8.48	Normal	Belgian database
Replacement	4.47	3.53	5.41	Normal	
Utility weights					
OPT	0.68	0.63	0.73	Beta	Cleland et al., 2005[8]; Calvert et al., 2005[11]; Feldman et al., 2005[9] and own assumptions.
CRT-P	0.78	0.73	0.83	Beta	
CRT-D	0.78	0.73	0.83	Beta	
Hospitalization primo implantation or replacement	0.46	0.41	0.51	Beta	
Costs**					
Primo implantation					
CRT-P	9,398 €	8,859 €	9,936 €	Normal	Belgian database, reimbursement tariffs and own adaptions.
CRT-D	23,380 €	22,842 €	23,919 €	Normal	
ICD	27,261 €	26,867 €	27,658 €	Gamma	KCE report ICDs[12]

Replacement					
CRT-P	9,061 €	8,267 €	9,856 €	Normal	Belgian database, reimbursement tariffs and own adaptions.
CRT-D	21,905 €	21,111 €	22,700 €	Normal	
Hospitalization	5,777 €	1,129 €	17,807 €	Gamma	Technical cel (APR-DRG 194 "heart failure")
Follow-up medication (monthly cost)	30.88 €	29.85 €	31.82 €	Beta for volumes	Belgian database (volumes) and BCFI (prices)
Follow-up visits (average monthly cost)	OPT	CRT-P	CRT-D		
GP, cardiologist (ECG, echo, integrity check)	52.98 €	71.87 €	90.77 €	Beta for volumes	Expert opinion
Cross-over/upgrade					
OPT - ICD	0.0015	-50%	+50%	Uniform	Bond et al., 2009[13]
CRT-P - CRT-D	0.0005	-50%	+50%	Uniform	

*: 95%CI, unless otherwise mentioned; **: Unless otherwise stated in the text, the year of costs reflects 2008 values. APR-DRG: All Patient Refined Diagnosis Related Groups; BCFI: Belgian Centre for Pharmacotherapeutic Information; CRT-P/D: cardiac resynchronisation therapy (CRT) both with pacemaker (CRT-P) and additionally including a defibrillator (CRT-D); ECG: electrocardiogram; GP: general practitioner; ICD: implantable cardioverter defibrillator; OPT: optimal pharmacologic treatment.

Hospitalisations

Hospitalisation rates were based on the COMPANION trial as reported by Feldman et al.[9] The monthly probability of hospital admission was estimated to be 0.117 for the OPT group, 0.098 (p=0.172) for CRT-P and 0.097 (p=0.141) for the CRT-D group (Table 1). The uncertainty

around these numbers was accounted for with a normal distribution. In our reference case, the hospitalisation rates were assumed to be constant over the full time horizon. This was subsequently altered during a scenario analysis.

Costs

An average cost of €23,380 (95%CI of the mean 22,842 - 23,919) for a primo CRT-D implantation was obtained from the actual hospital billing data of 342 Belgian CRT-D primo implantations that occurred during the period 2008 until mid 2009. This cost was modelled with a normal distribution (Table 1). The implantation cost of a primo CRT-P was inferred by subtracting the cost difference from the CRT-D implantation cost. Based on the reimbursement tariffs, the price for CRT-P and CRT-D, including leads, was €7,187 and €21,170, respectively.[7] As such, the average cost for CRT-P implantation was €9,398 (95%CI of the mean €8,859 - 9,936).

A similar approach was used for the cost of a device replacement. Based on Belgian data (n = 121), the CRT-D replacement cost was €21,905 (95%CI of the mean €21,111 - €22,700). With a price difference between the CRT-P and CRT-D device of €12,844, this amounted to €9,061 (95%CI of the mean €8,267 - €9,856) for CRT-P. Service life was equalled to the average of expert opinion-based service lives encountered in other studies,[9, 10] i.e. 75 months for CRT-P and 60 months for CRT-D. This assumption was altered in various scenario analyses.

Data from the Belgian Technical Cell (www.tct.fgov.be) served as the source for obtaining hospitalisation costs. The cost for “APR-DRG 194 Heart Failure” was on average €5,529 (90%CI 1,233 - 14,132) per hospitalisation based on data from more than 19,000 hospitalisation episodes in the year 2007. This cost was included as a gamma distribution and adjusted to 2008 values (Consumer Price Index of 104.5% or on average €5,777) (Table 1).

Prescription medication use was taken from the available data on the Belgian CRT population, right before implantation.[7] The amount and type of drugs were assumed to remain the same after implantation on a per patient base. Prescription medication costs were based on the cheapest formulation as indicated by the Belgian Centre for Pharmacotherapeutic Information, www.bcfi.be (accessed November 2010). The percentage of users was included as a beta distribution with parameters reflecting the values of the Belgian CRT sample. The average monthly medication cost was €30.88 per patient (95%CI 29.85 - 31.82) (Table 1). Details are presented as data supplement.

Based on expert opinion, we assumed patients consulted their cardiologist four times a year at €34.02 per consultation, and received GP visits at €19.37 per visit for the remaining eight months of the year. This was modelled applying a beta distribution with the minimum and maximum ±50% above/under the average. For every consultation an ECG (€16.94) and echocardiographic examination (€69.24) were billed as well. A CRT integrity check was also counted at €56.68 for CRT-P and €113.36 for CRT-D systems. As such, the monthly visit costs for OPT, CRT-P and CRT-D were respectively €52.98, €71.87 and €90.77 (Table 1).

Finally, the model also included a possibility for cross-over or upgrade. Patients in the OPT group could receive an ICD, whereas patients in the CRT-P group could be upgraded to CRT-D. Medical therapy and CRT recipients received an ICD in the model of Bond et al.[13]/Fox et al.[10] as soon as they survived a serious arrhythmic event. Based on their model, we included upgrade probabilities of 0.0015 and 0.0005 per month for the OPT and CRT-P group, respectively (Table 1). These probabilities were multiplied with a uniform distribution (0.5-1.5) to reflect the large uncertainty around these numbers. The cost of an ICD implantation was based on another Belgian ICD study and amounts to €27,261 (95%CI 26,867 - 27,658)[12]. We preferred not to index this cost since the reimbursement price for the device has decreased since then. For an upgrade from CRT-P to CRT-D, the cost of a CRT-D replacement was taken

into account. Cross-over- or upgrade-related procedural deaths were not explicitly accounted for since we assumed these to be reflected in the initial intention-to-treat mortality rates.

Utilities

Utility values were based on the studies of Cleland et al.,[8] Calvert et al.[11] and Feldman et al.[9] The baseline out-of-hospital utility was set to 0.68 (Table 1).[9] 2) The utility improvement in the CRT-P/D groups was estimated to amount to 0.1,[8, 9, 11] resulting in a utility weight of 0.78. An average utility weight of 0.46 was incorporated during the hospital stay of the initial and replacement implantations, which averaged respectively 7.34 days and 4.47 days in the Belgian CRT sample (Table 1). Details of the studies that support these utility values are briefly outlined in the data supplement on utilities.

Sensitivity and scenario analyses

Results of the probabilistic model are presented on the cost-effectiveness plane and as cost-effectiveness acceptability curves. Several scenario analyses are performed for mortality rates, hospitalizations, discount rates, and device service life.

RESULTS

According to the model, the undiscounted life expectancy is 4.6 years for the OPT group. CRT-P increases life expectancy with 1.31 years (95%CI -0.04 – 3.21). CRT-D adds another 0.8 years (95%CI -1.40 – 2.95) on top of CRT-P. If quality of life changes are taken into account, this becomes 1.47 QALYs (95%CI 0.39 – 3.00) and 0.63 QALYs (95%CI -1.18 – 2.38), respectively. This results in a discounted incremental effect adjusted for quality of life of 1.31 QALYs (95%CI 0.36 – 2.64) and 0.55 QALYs (95%CI -1.02 – 2.07), respectively.

The average incremental cost is less than €15,000 for CRT-P versus OPT. In combination with the discounted gain in life expectancy, this results in an average ICER of about €12,800/LYG. If

QoL-adjustments are taken into account, this becomes €11,200/QALY gained. The ICER of CRT-D versus OPT is higher than that of CRT-P versus OPT, thus calculating the ICER on the efficiency frontier, CRT-P becomes its economic justified comparator. The total incremental cost of CRT-D versus CRT-P is on average more than €30,000. The ICER becomes on average €44,100/LYG or €56,600/QALY gained. More details and confidence intervals are available in the data supplements.

Figure 2 shows the cost-effectiveness plane; on top both CRT-P and CRT-D versus OPT (incremental effects on the x-axis expressed as QALYs gained), while at the bottom CRT-P becomes the comparator for CRT-D. The scatter plot clearly shows the impact of considering CRT-P as the comparator for CRT-D. If we compare CRT-D with OPT, then the simulations are completely in the first quadrant. In contrast, if we compare CRT-D with CRT-P, about 23% of the simulations are situated in the dominated quadrant (being more costly and less effective).

Insert Figure 2 around here

For each of the 1000 simulations, ICERs are calculated, allowing to express results as the probability that the three alternatives are considered cost-effective depending on the WTP for a QALY. Figure 3 shows these cost-effectiveness acceptability (CEA)-curves. OPT is the preferred option if the WTP for a QALY gained is less than €11,000. Above this threshold, CRT-P is most probably the best alternative with a probability of about 90% at a threshold of about €21,000 per QALY gained. If this willingness is more than €30,000, the probability that OPT is chosen is almost nil. This WTP has to increase to more than €56,000 per QALY gained for CRT-D to have a probability of more than 50% for being considered a cost effective alternative.

The fact that there is still a probability that CRT-P is cost effective at this high WTP threshold illustrates the uncertainty around the incremental benefit of CRT-D versus CRT-P.

Insert Figure 3 around here

Scenario analyses on mortality, hospitalisation and discount rates revealed that the results for CRT-P versus OPT can be considered robust. The difference in cost-effectiveness between CRT-P and CRT-D is mainly determined by the threefold higher device price for a CRT-D versus CRT-P. Furthermore, at current price differences between CRT-P and CRT-D, small incremental benefits of CRT-D versus CRT-P result in relatively unfavourable cost-effectiveness ratios for CRT-D. For the results of these scenario analyses, we refer to the data supplements and the full HTA report.[7]

DISCUSSION

In previously published health economic evaluations of CRT, ICERs vary considerably, both for CRT-P versus OPT (from €3,600[14] to $108,000[15] per QALY gained) and for CRT-D versus CRT-P (from £40,200[13] to $172,300[9] per QALY gained). A detailed overview of these evaluations is available in the full HTA report.[7] Since costs and resource use may widely vary across countries and because of methodological considerations, results might not be applicable to Belgian practice, and thus it was decided to perform a health economic evaluation of CRT from a Belgian health care payer perspective.

Compared with OPT, on average 1.31 QALYs are gained with CRT-P at an additional cost of €14,700, resulting in a relatively robust ICER of about €11,200/QALY. Reimbursing CRT-P can

thus be considered as efficient use of limited sources if the WTP is higher than €11,000 for a QALY gained. Compared to CRT-P, CRT-D provides on average 0.55 QALYs at an extra cost of €30,900 or an average ICER of €57,000/QALY. This result largely depends on the added value of CRT-D versus CRT-P. Based on our indirect comparison CRT-D was dominated by CRT-P in about 23% of the simulations. Current evidence is insufficient to show the superiority of CRT-D over CRT-P. With a threefold higher device cost, CRT-D's cost-effectiveness is questionable.

All economic evaluations, including our own model, are subject to a number of common limitations. Firstly, there is the short-term follow-up of the trials necessitating extrapolation assumptions. Secondly, the economic evaluations are limited by the external validity of the trial results. The technical skills of providers, patient selection and differences in the optimal treatment regimen may vary in real world practice and affect the clinical effectiveness of the therapy. For example, only experienced providers participated in the trials. Therefore, it is possible that the complication rates are not generalizable to other, less experienced, provider settings and results of the economic models may be biased in favour of CRT.

Furthermore, economic evaluations are limited by the way QoL was included. Generic utility instruments to measure QoL are not systematically used in trials. In contrast to this economic evaluation, several studies include utility values by NYHA class rather than for the different treatment groups. The validity of this approach depends on a double link. Firstly, the link between the treatment and the outcome (in terms of NYHA class, which is a subjective measure for functional disability). Secondly, the link between NYHA class and QoL. Such indirect determination bears an increased risk of inaccuracy. Since NYHA class utility estimates vary substantially between publications,[7] results can be somewhat manipulated. It would be useful to include more systematically a generic utility instrument to measure QoL in trials. Calvert et al.[11] showed that the EQ-5D appears to be an acceptable valid measure for use in patients

with HF. Nevertheless, a minority of studies include such an instrument in addition to disease-specific instruments in their research protocol.

In our assessment of the cost-utility of CRT we found that, compared to OPT, CRT-P has a better cost-effectiveness ratio than CRT-D. Therefore, the relevant comparator for assessing the cost-effectiveness of CRT-D, which is marginally and non-significantly more efficacious regarding mortality than CRT-P, is therefore CRT-P. The chosen comparator obviously may have a large impact on the resulting ICER. Feldman et al.[9] for instance compared both CRT-P and CRT-D with OPT, but did not compare CRT-D with CRT-P. The ICER of CRT-D compared to OPT as reported by Feldman et al. was $43,000 per QALY, whereas the ICER compared to CRT-P would have resulted in $172,300 per QALY. Economic evaluations should be performed on the so-called “efficiency frontier” and choosing an inappropriate comparator may influence results in a misleading way and alter conclusions.

A direct comparison of the performance of CRT-P vs. CRT-D has not yet been performed. A Bayesian network meta-analysis of randomised controlled trials indicated that evidence is insufficient to show the superiority of CRT-D over CRT-P in these patients.[16] The added value of CRT-D versus CRT-P in patients with moderate to severe HF is unknown and may be an interesting topic for further research in a randomized controlled trial, especially because of the threefold higher price for a CRT-D device versus CRT-P.

CONTRIBUTOR STATEMENT

MN carried out the economic analysis and drafted the paper. SS and CO performed an economic literature review to collect relevant data. SD prepared the demand for the Belgian commission for the protection of personal data. CC and SD analysed the Belgian data. CD and HV provided medical advice and performed a medical literature review in search for relevant data. All authors participated in revising the draft paper and approved the version to be published. MN is guarantor for the paper.

COMPETING INTERESTS

The authors have no conflicts of interest relevant to the content of this study.

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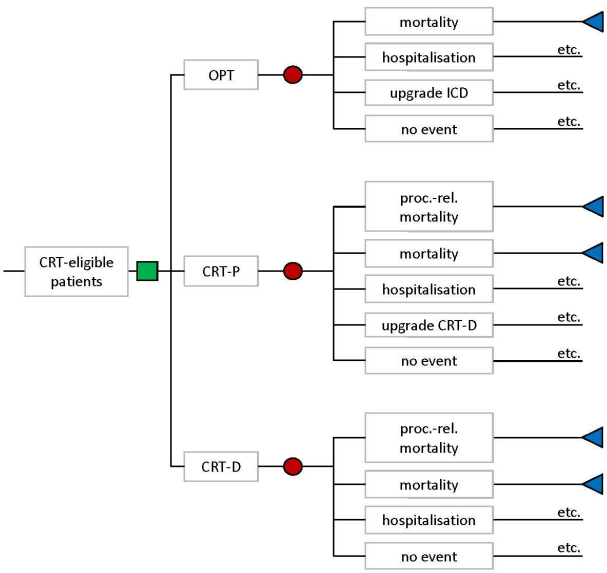
IMAGES

Uploaded as separate files:

Figure 1: CRT-P/D decision model

Figure 2: Cost-effectiveness planes CRT-P/D versus OPT (top) and CRT-D versus CRT-P (bottom)

Figure 3: Cost-effectiveness acceptability curves for the three alternative treatment options (OPT, CRT-P and CRT-D)



CRT-P/D decision model
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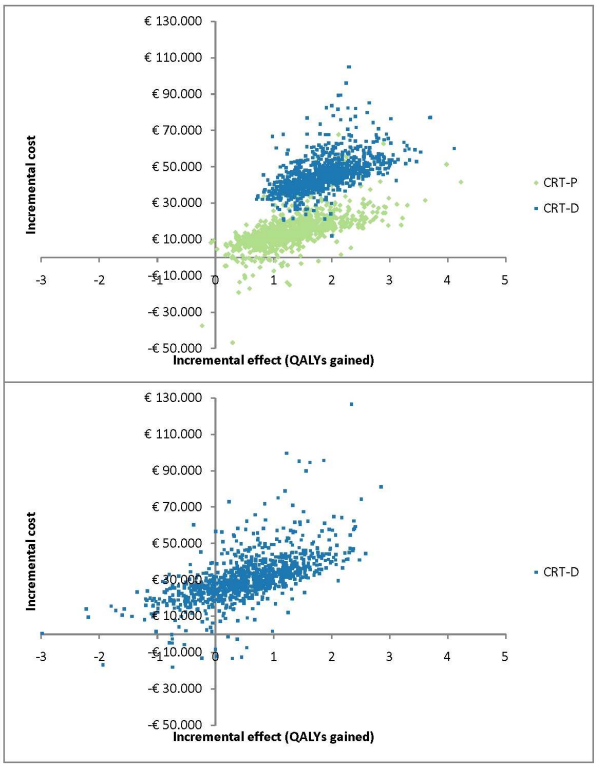
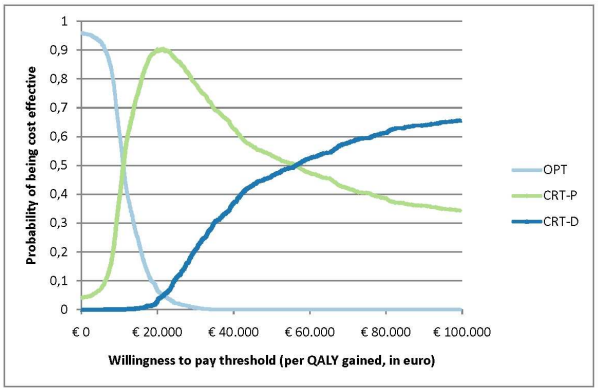


139x198mm (300 x 300 DPI)



Cost-effectiveness acceptability curves for the three alternative treatment options (OPT, CRT-P and CRT-D)
139x198mm (300 x 300 DPI)